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Original article

Associations between glycated albumin or hemoglobin A1c and the presence of coronary artery disease

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ABSTRACT

Objective: We investigated the associations between serum levels of glycated albumin (GA) or hemoglobin A1c (HbA1c) and the presence of coronary artery disease (CAD) in patients who underwent coronary computed tomography angiography (CTA).

Methods and results: The study consisted of 244 consecutive patients who underwent CTA and in whom we could measure the levels of both GA and HbA1c. Any narrowing of the normal contrast-enhanced lumen to >50% that could be identified in multiplanar reconstructions or cross-sectional images by CTA was defined as significant stenosis in CAD. We divided the patients into two groups: CAD group ($n = 72$) and non-CAD group ($n = 172$), as assessed by CTA. The CAD group showed significantly higher GA and HbA1c than the non-CAD group. GA and HbA1c showed a positive correlation ($r = 0.551$, $p < 0.0001$). A multivariate logistic regression analysis was performed to examine the associations between the presence of CAD and age, gender, body mass index, and coronary risk factors (hypertension, dyslipidemia, and smoking), in addition to GA and HbA1c. Age [odds ratio (OR): 1.04, $p = 0.02$], gender (OR: 2.84 $p = 0.01$), hypertension (OR: 3.20, $p = 0.01$), and GA (OR: 1.16, $p = 0.03$) were identified as significant independent variables that predicted the presence of CAD. In particular, GA (OR: 1.30, $p = 0.02$) was the only predictor of the presence of CAD in the diabetes mellitus group by a multivariate logistic regression analysis. We defined the cut-off value of GA for the prediction of CAD in patients with diabetes as 17.9% (sensitivity 0.639, specificity 0.639) by a receiver-operating characteristic curve analysis.

Conclusion: GA may be superior to HbA1c as a marker for evaluating the presence of CAD.

Introduction

Serum levels of hemoglobin A1c (HbA1c) are strongly correlated with average blood glucose (BG) levels [1,2], whereas serum levels of glycated albumin (GA) reflect postcibal BG levels [2]. Some previous studies have indicated that impaired glucose tolerance makes a greater contribution to the risk of coronary artery disease (CAD) than impaired fasting glucose [3,4]. In addition, patients with impaired glucose tolerance who are treated with acarbose show a significant reduction in the risk of CAD [5]. Although HbA1c, fasting BG levels, and mean BG concentrations are not correlated with oxidative stress, the mean amplitude of glycemic excursions and postcibal BG levels are positively correlated with oxidative stress, which indicates that the target of therapy should be not only HbA1c, but also acute glucose fluctuation in patients with type 2 diabetes mellitus (DM) [6]. In addition, GA is more strongly correlated with microvascular conditions than HbA1c [7], and an increase in serum GA is also associated with the presence and severity of CAD in type 2 DM [8]. These reports indicated that GA may be superior to HbA1c as a predictor of CAD. Therefore, we investigated the associations between serum levels of GA or HbA1c and the presence of CAD in patients who underwent coronary computed tomography angiography (CTA), and considered whether GA is more useful than HbA1c for predicting the presence of CAD.

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Methods

Study subjects

Two hundred and forty-four consecutive subjects who were clinically suspected to have CAD were enrolled. All subjects underwent CTA and their GA and HbA1c levels were measured. Patients in whom we could not evaluate coronary stenosis due to severe calcification, or who had acute coronary syndrome, Kawasaki disease, or Marfan syndrome were excluded. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their written informed consent to participate.

Evaluation of coronary stenosis using CTA

We evaluated coronary stenosis using CTA as previously described [9]. Briefly, all patients were scanned by 64-multi-detector row computed tomography (MDCT) on an Aquilion 64 (Toshiba, Tokyo, Japan). The use of β-blocker and nitroglycerin before scanning was left to the physician's discretion. A 70-ml bolus of contrast medium (Omnipaque, 350 mg iodine/ml, Daiichi Sankyo Co. Ltd., Tokyo, Japan) was injected at a flow rate of 3.6 ml/s, and followed by 35 ml of contrast agent and 30 ml of saline solution, each at a flow rate of 1.8 ml/s, with a dual injector. The region of interest was placed within the ascending aorta, and the scan was started when the CT density reached 100 Hounsfield Units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and the diaphragm with the following parameters: collimation width 0.5 mm, rotation speed 0.4 s/rotation, tube voltage 135 kV, and effective tube current 360 mA. All segments were assessed according to the 15-segment American Heart Association coronary artery model [10]. Overall, 15 coronary artery segments were assessed in all patients. Any narrowing of the normal contrast-enhanced lumen to >50% that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant stenosis in CAD.

Evaluation of CAD risk factors

Age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), GA, HbA1c and BG, smoking status (current vs. nonsmoker), family history [myocardial infarction (MI), angina pectoris, or sudden death], and medication use were evaluated as risk factors for CAD in all patients.

BMI was calculated as weight (kg)/height (m^2). BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 min of rest. The characteristics

Table 1
Characteristics of patients in all, CAD and non-CAD groups.

Variables	All ($n=244$)	CAD ($n=72$)	Non-CAD ($n=172$)
Age (years)	66 (59–72)	68 (61–74)*	64 (57–71)
Male (%)	57	67*	53
BMI (kg/m^2)	24 ± 4	24 ± 4	24 ± 4
Smoking (%)	48	50	48
FH (%)	28	26	29
HTN (%)	75	89**	69
SBP (mmHg)	133 (123–146)	135 (123–147)	132 (122–145)
DBP (mmHg)	77 ± 12	76 ± 13	77 ± 12
DL (%)	77	79	76
LDL-C (mg/dl)	110 ± 30	108 ± 27	111 ± 32
HDL-C (mg/dl)	49 (43–60)	47 (40–56)**	51 (44–62)
TG (mg/dl)	120 (87–162)	128 (93–188)	114 (80–154)
TC (mg/dl)	195 ± 36	189 ± 33	198 ± 36
HU (%)	18	18	18
UA (mg/dl)	6.0 (5.0–6.0)	5.0 (4.0–6.0)	6.0 (5.0–7.0)
DM (%)	30	50**	21
Random BG (mg/dl)	101 (93–115)	112 (96–143)**	100 (93–108)
HbA1c (%)	5.9 (5.6–6.4)	6.3 (5.8–7.2)**	5.8 (5.6–6.2)
GA (%)	15.6 (14.3–17.1)	16.7 (15.3–19.0)**	15.3 (14.0–16.9)
CKD (%)	31	30	33
eGFR (ml/min/1.73 m^2)	68 ± 15	69 ± 15	68 ± 15
PAD (%)	2	3	2
Medications			
ARB/ACE-I (%)	42	50	38
CCB (%)	38	50*	33
BB (%)	14	14	15
DU (%)	12	11	12
Statin (%)	35	44*	31
Insulin (%)	4	4	4
SU (%)	8	17**	5
Biguanide (%)	9	17**	6
DPP4-I	10	15	8

Continuous variables are expressed as mean ± SD. When continuous variables did not show a normal distribution, the variables are expressed as a median value and interquartile range.
CAD, coronary artery disease; BMI, body mass index; FH, family history; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; HU, hyperuricemia; UA, uric acid; DM, diabetes mellitus; BG, blood glucose; HbA1c, glycosylated hemoglobin A1c; GA, glycated albumin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, β-blocker; DU, diuretic; SU, sulfonylurea; DPP4-I, dipeptidyl-peptidase 4 inhibitor.
* $p<0.05$ vs. non-CAD group.
** $p<0.01$ vs. non-CAD group.

of the patients with regard to history of hypertension (HTN), dyslipidemia (DL), DM, and history of smoking were obtained from medical records. Patients who had a current SBP ≥140 mmHg and/or DBP ≥90 mmHg or who were receiving antihypertensive therapy were considered to have HTN. Patients with LDL-C ≥140 mg/dl, TG ≥150 mg/dl, and/or HDL-C <40 mg/dl, or who were receiving lipid-lowering therapy were considered to have DL [11]. Patients with random BG ≥200 mg, fasting BG ≥126 mg, HbA1c ≥6.5% or who were taking a glucose-lowering drug were considered to have DM. Hyperuricemia (HU) was defined as a serum UA level of ≥7.0 mg/dl or the administration of UA-lowering drugs.

Statistical analysis

The statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) at Fukuoka University. Continuous variables are shown as the mean ± standard deviation. Categorical and continuous variables were compared between the groups by a chi-square analysis and *t*-test, respectively. When continuous variables did not show a normal distribution expressed as a median value and interquartile range, we performed a Wilcoxon rank-sum test. The Spearman rank correlation coefficient was used to evaluate associations between the groups. We used a multiple logistic regression analysis for the multivariate analysis to evaluate independent predictors of CAD and selected age, gender, BMI, and coronary risk factors (smoking, HTN, DL) in addition to GA and HbA1c as independent variables. A receiver-operating characteristic (ROC) curve analysis was used to determine the cut-off values of GA and HbA1c to distinguish between patients with and without CAD at the highest possible sensitivity and specificity levels. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics

Table 1 shows the patient characteristics in all patients and in the CAD and non-CAD groups. The CAD group showed a significantly higher age, percentage of males, prevalence of HTN and DM, BG, HbA1c, GA, and use of calcium channel blocker (CCB), statin, sulfonylurea (SU), and biguanide, and a significantly lower level of HDL-C than the non-CAD group. As shown in Table 2, we divided the patients with DM ($n = 72$) into two groups: CAD ($n = 36$) and non-CAD ($n = 36$). The CAD group showed a significantly higher GA level. However, there were no significant differences in HbA1c or the use of glucose-lowering drugs between the two groups. Next, we divided the patients without DM ($n = 172$) into two groups: CAD ($n = 36$) and non-CAD ($n = 136$) (Table 3). The CAD group was significantly older and had a higher incidence of HTN and use of CCB, and a significantly lower level of

Table 2
Characteristics of patients with DM in all, CAD and non-CAD groups.

Variables	All ($n = 72$)	CAD ($n = 36$)	Non-CAD ($n = 36$)
Age (years)	66 ± 9	67 ± 9	65 ± 10
Male (%)	69	72	67
BMI (kg/m^2)	25 ± 4	25 ± 3	25 ± 5
Smoking (%)	61	58	64
FH (%)	18	22	14
HTN (%)	88	92	83
SBP (mmHg)	141 (126–150)	142 (123–151)	140 (127–148)
DBP (mmHg)	79 ± 13	77 ± 14	80 ± 12
DL (%)	79	83	75
LDL-C (mg/dl)	103 ± 27	106 ± 24	99 ± 30
HDL-C (mg/dl)	49 (42–56)	48 (45–53)	49 (41–59)
TG (mg/dl)	119 (96–179)	137 (109–189)	109 (93–145)
TC (mg/dl)	184 ± 31	188 ± 30	180±31
HU (%)	13	11	15
UA (mg/dl)	5.0 (5.0–6.0)	5.2 (4.4–6.1)	6.0 (5.0–7.0)
DM (%)	100	100	100
Random BG (mg/dl)	128 (104–150)	139 (113–164)	115 (101–140)
HbA1c (%)	6.9 (6.5–7.6)	7.2 (6.6–7.7)	6.8 (6.4–7.3)
GA (%)	18.0 (16.2–20.9)	18.5 (16.6–21.8)*	16.8 (16.0–19.1)
CKD (%)	38	28	44
eGFR (ml/min/1.73 m^2)	67 ± 16	71 ± 17	65 ± 14
PAD (%)	3	6	0
Medications			
ARB/ACE-I (%)	47	56	39
CCB (%)	39	47	31
BB (%)	11	6	17
DU (%)	14	11	17
Statin (%)	43	50	36
Insulin (%)	13	8	17
SU (%)	28	33	22
Biguanide (%)	31	33	28
DPP4-I (%)	35	31	39

Continuous variables are expressed as mean SD. When continuous variables did not show a normal distribution, the variables are expressed as a median value and interquartile range.
CAD, coronary artery disease; BMI, body mass index; FH, family history; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; HU, hyperuricemia; UA, uric acid; DM, diabetes mellitus; BG, blood glucose; HbA1c, glycosylated hemoglobin A1c; GA, glycated albumin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, β-blocker; DU, diuretic; SU, sulfonylurea; DPP4-I, dipeptidyl-peptidase 4 inhibitor.
* $p < 0.05$ vs. non-CAD.

Table 3
Characteristics of patients without DM in all, CAD and non-CAD groups.

Variables	All (n = 172)	CAD (n = 36)	Non-CAD (n = 136)
Age (years)	65 (58–72)	69 (61–75)*	64 (56–72)
Male (%)	52	61	49
BMI (kg/m^2)	23 (21–26)	24 (21–26)	23 (21–26)
Smoking (%)	43	42	43
FH (%)	32	31	33
HTN (%)	70	86*	65
SBP (mmHg)	131 (122–143)	134 (124–139)	131 (120–144)
DBP (mmHg)	76 ± 12	74 ± 12	76 ± 12
DL (%)	76	75	77
LDL-C (mg/dl)	113 ± 35	111 ± 30	114 ± 31
HDL-C (mg/dl)	50 (43–62)	45 (27–56)**	51 (45–63)
TG (mg/dl)	122 (80–160)	126 (88–180)	119 (79–155)
TC (mg/dl)	200 ± 43	191 ± 37	202 ± 36
HU (%)	20	26	18
UA (mg/dl)	6.0 (4.0–7.0)	6.0 (4.0–7.0)	6.0 (4.5–6.0)
DM (%)	0	0	0
Random BG (mg/dl)	98 (92–104)	99 (93–112)	98 (92–103)
HbAlc (%)	5.7 (5.5–6.0)	5.8 (5.6–6.0)	5.7 (5.5–5.9)
GA (%)	14.9 (13.8–16.5)	15.5 (14.4–16.9)	14.8 (13.7–16.3)
CKD (%)	27	25	29
eGFR (ml/min/1.73 m^2)	68 ± 15	67 ± 12	69 ± 16
PAD (%)	2	0	2
Medications			
ARB/ACE-I (%)	40	44	38
CCB (%)	37	53*	33
BB (%)	16	22	14
DU (%)	11	11	11
Statin (%)	31	39	29

Continuous variables are expressed as mean SD. When continuous variables did not show a normal distribution, the variables are expressed as a median value and interquartile range.
CAD, coronary artery disease; BMI, body mass index; FH, family history; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; HU, hyperuricemia; UA, uric acid; DM, diabetes mellitus; BG, blood glucose; HbA1c, glycosylated hemoglobin A1c; GA, glycated albumin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, β-blocker; DU, diuretic; SU, sulfonylurea; DPP4-I, dipeptidyl-peptidase 4 inhibitor.
* $p < 0.05$ vs. non-CAD.
** $p < 0.01$ vs. non-CAD.

HDL-C than the non-CAD group. There were no significant differences in HbA1c or GA between the groups.

Relationships between GA or HbA1c and other factors

HbA1c and GA showed a significant positive correlation (Fig. 1A). Since GA showed a negative correlation with BMI [12], we examined the correlations between GA and BMI or visceral fat area. However, neither factor was significantly correlated with GA (BMI, $r = -0.025$, $p = 0.692$; visceral fat area, $r = 0.017$, $p = 0.786$). On the other hand, GA showed a positive correlation with age (Fig. 1B). A ratio of GA to HbA1c (GA/HbA1c), but not HbA1c alone ($r = 0.035$, $p = 0.577$), showed a similar significant correlation (Fig. 1C).

Predictors of the presence of CAD in all patients and in the DM and non-DM groups

Next, we analyzed the predictors of the presence of CAD in all patients using independent variables by a logistic regression

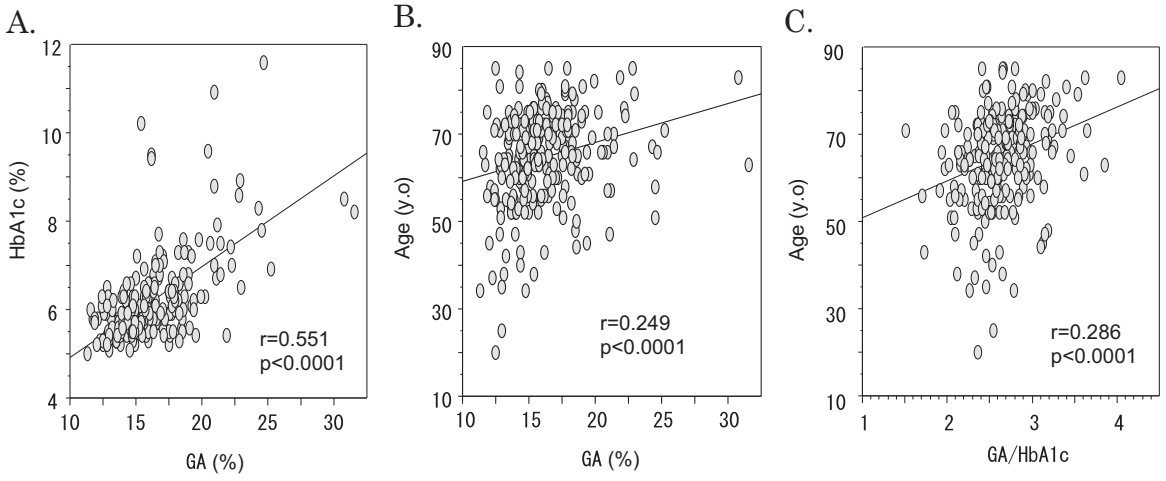

Fig. 1. Association between GA and HbA1c (A). Associations between age and GA (B) or the ratio of GA to HbA1c (GA/HbA1c) (C). GA, glycated albumin; HbA1c, hemoglobin A1c.

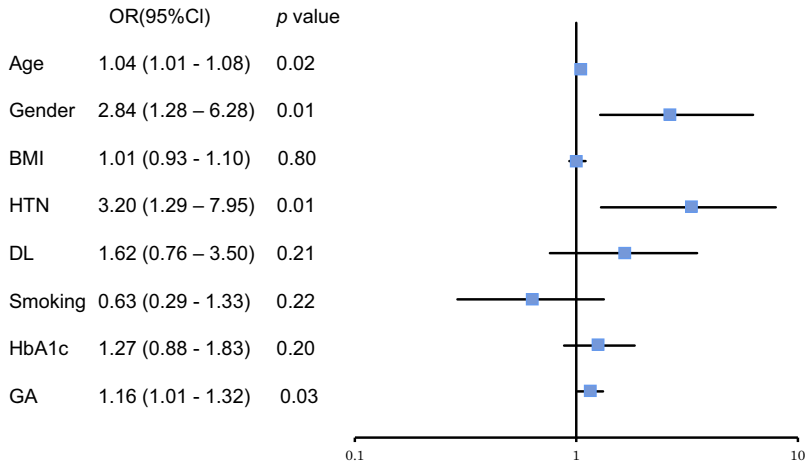

Fig. 2. Logistic regression analysis for the presence of coronary artery disease in all patients using independent variables. BMI, body mass index; HTN, hypertension; DL, dyslipidemia; HbA1c, hemoglobin A1c; GA, glycated albumin.

analysis (Fig. 2). We selected age, gender, BMI, coronary risk factors (smoking, HTN, DL), GA, and HbA1c as independent variables. CAD was independently associated with GA, in addition to age, gender, and HTN. We also examined the predictors of the presence of CAD in patients with or without DM using the same independent variables by a logistic regression analysis (Figs. 3 and 4). GA was the only predictor of the presence of CAD in the DM group. In the non-DM group, age and gender were associated with the presence of CAD.

Cut-off values of GA and HbA1c for the diagnosis of CAD in the DM group

A ROC curve analysis in the DM group showed that the area under the curve for GA (0.644) was greater than that for HbA1c (0.594) (Fig. 5). The cut-off levels of GA and HbA1c that gave the greatest sensitivity and specificity for the diagnosis of CAD in the DM group were 17.9% (sensitivity 0.639, specificity 0.639) and 6.9% (sensitivity 0.667, specificity 0.611), respectively.

Discussion

In this study, we determined whether GA is more useful than HbA1c as a marker of the presence of CAD. As a result, we found that age, gender, HTN, and GA level were independent predictors of the presence of CAD in all patients. Age, gender, and HTN are well-known essential risk factors for CAD. Although GA was not a significant predictor in the non-DM group, age and gender were independent predictors of the presence of CAD. As expected, GA was the only independent predictor of the presence of CAD in the DM group. This result indicated that GA may be superior to HbA1c as a marker for evaluating the presence of CAD in patients with DM.

Since the half-time of serum albumin is shorter than that of erythrocytes, GA reflects glycemic control over a short period in comparison with HbA1c [13,14]. Thus, GA can be generally used for effective decision-making after starting or changing medications, and GA has also been reported to be useful for glycemic control in pregnant patients and patients undergoing dialysis [15,16]. It is generally known that GA and HbA1c show a positive correlation, as seen in this study (Fig. 1A). There is an issue of whether GA is a better predictor of CAD than HbA1c, although there is a significant positive correlation between GA and HbA1c. Generally, HbA1c shows a good correlation with mean BG levels [1,2], whereas GA is more closely related to postcibal BG levels [2]. Selvin et al. previously reported that GA is a more useful predictor for the presence of microangiopathy than HbA1c [7]. It is difficult to analyze postcibal BG precisely in outpatients at every visit, whereas the measurement of GA is easy and not influenced by

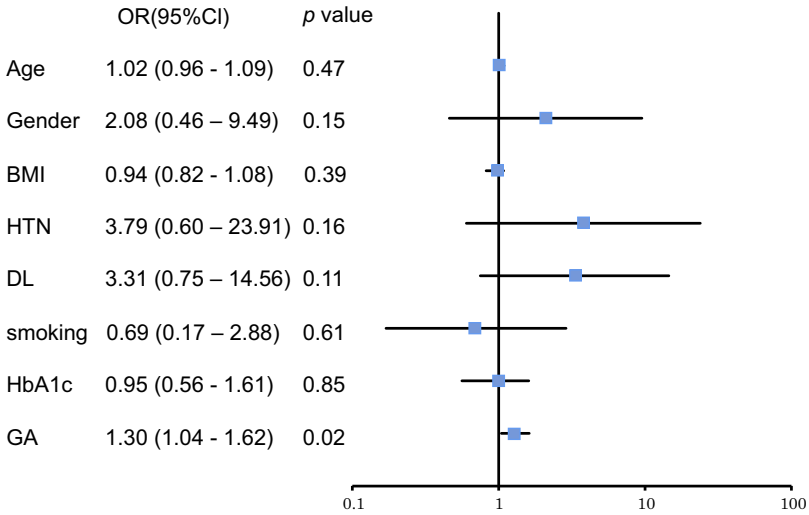

Fig. 3. Logistic regression analysis for the presence of coronary artery disease in patients with diabetes mellitus using independent variables. BMI, body mass index; HTN, hypertension; DL, dyslipidemia; HbA1c, hemoglobin A1c; GA, glycated albumin.

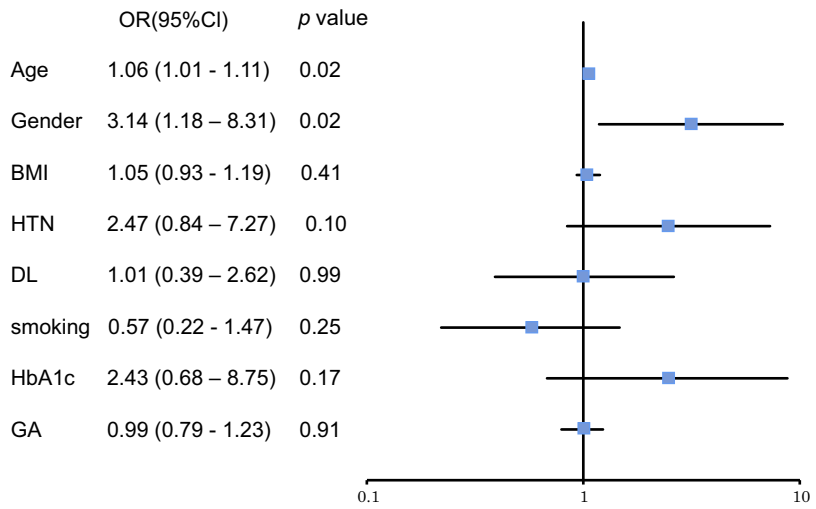

Fig. 4. Logistic regression analysis for the presence of coronary artery disease in patients without diabetes mellitus using independent variables. BMI, body mass index; HTN, hypertension; DL, dyslipidemia; HbA1c, hemoglobin A1c; GA, glycated albumin.

meals. Sakuma et al. reported that HbA1c correlated most closely with the average fasting BG over the previous 4 weeks and that GA correlated most closely with the average 2-h postcibal BG after breakfast over the previous 4 weeks [17]. GA is more closely related to glycemic fluctuation and excursion than HbA1c in diabetic patients with poor glycemic control using a continuous glucose-monitoring system [18]. Moreover, postcibal hyperglycemia contributes more to cardiovascular events and the risk of death than fasting hyperglycemia [3–5]. The ACCORD and ADVANCE trials indicated that strict glycemic control as assessed by HbA1c did not prevent cardiovascular events [19,20]. These reports may explain why GA was a useful predictor for the presence of CAD in this study.

Another important observation in this study was that GA and GA/HbA1c, but not HbA1c, showed a positive correlation with age. GA/HbA1c and age have been reported to have a positive correlation [21]. In older subjects who show a decreased capacity of skeletal muscle, the metabolism of glucose after a meal is reduced, as is the additional secretion of insulin. Since postcibal BG tends to be higher than fasting BG in older subjects [22], and since GA levels reflect postcibal BG levels, GA levels reflect the state of older subjects more precisely than HbA1c.

The cut-off levels of GA and HbA1c for the diagnosis of CAD in the DM group were 17.9% and 6.9%, respectively. The cut-off level of HbA1c (6.9%) does not contradict the target value of HbA1c <7.0 (prevention of diabetic complications) according to the Japan Diabetes Society. It is possible that glycemic control that aims to achieve GA <17.9% may be effective for the prevention of cardiovascular events.

Study limitations

This study has several important limitations. First, the sample size was relatively small, which limited our ability to determine significance. A large-scale prospective study will be needed to prove the utility of GA-targeting therapy. Second, MDCT is not a gold standard for the evaluation of CAD, although studies have shown that both its sensitivity and specificity were approximately

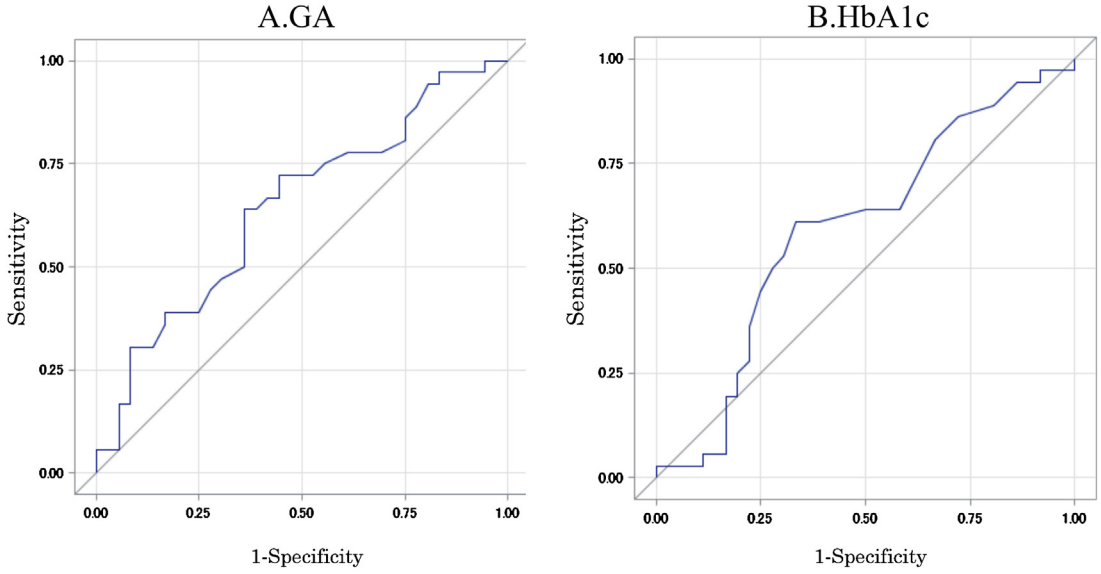

Fig. 5. Receiver-operating characteristic curve analysis for (A) glycated albumin (GA) and (B) hemoglobin A1c (HbA1c) for the presence of coronary artery disease in patients with diabetes mellitus.

95% of those for invasive coronary angiography for the identification of significant coronary stenosis [23,24]. Third, in the case of CTA in the morning, the patients did not eat breakfast. For examinations in the afternoon, they ate breakfast and did not eat lunch. Since we performed blood collection just before CTA, we could not measure fasting BS in all patients.

Conclusion

In this study, we showed that GA may be superior to HbA1c as a marker for evaluating the presence of CAD. In particular, GA was identified as the only significant independent variable for predicting the presence of CAD in the DM group. GA target therapy may be more effective for reducing the complications of arterial sclerosis than HbA1c target therapy.

Disclosure

K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K.S. is the Chairman of an Endowed Department, the ''Department of Molecular Cardiovascular Therapeutics'', supported by MSD, Co. Ltd. S.M. belongs to the Department of Molecular Cardiovascular Therapeutics, supported by MSD, Co. Ltd.

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